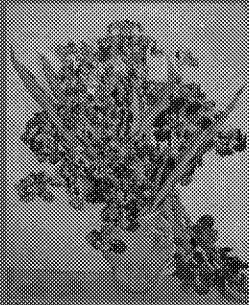
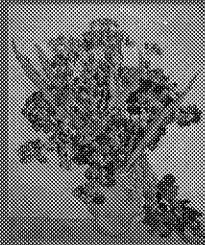


Improving IRIS:

We're on a Good Path – It's Just Uphill

Vincent Cogliano

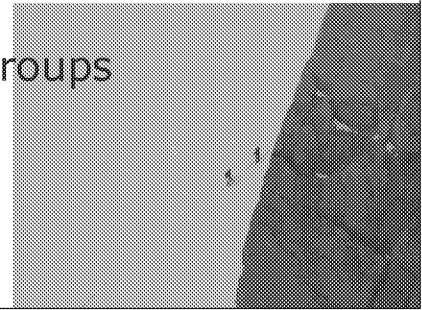


Overview

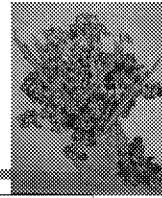


Suggested topic: *Your experience and vision/ approaches to ensure success for the IRIS program*

- Some experiences at IARC
- Approaches necessary for the success of IRIS
 - Adopt systematic review
 - Increase public engagement
 - Work through disciplinary workgroups
- Vision for the future



When I Arrived at IARC, They Had Been Under Fire



THE LANCET

Volume 361, No 9245, 2003

Transparency at IARC

The appearance in a number of the most respected of the international Agency for Research on Cancer (IARC) journals of the new Director-General of WHO, Dr. Gro Harlem Brundtland, was followed in 1995 by the publication of the first IARC monograph, a review of the epidemiological evidence on the carcinogenicity of asbestos. IARC also has other research, especially on cancer epidemiology and laboratory carcinogenesis. Starting last September, Dr. Brundtland began to move people around within the organization, and some of the moves have been reported in the press.

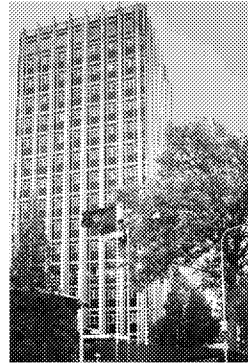
Dr. Brundtland's first move was to appoint Dr. Peter D. Jacobson as Deputy Director-General. Dr. Jacobson is a well-known epidemiologist and has been at IARC since 1980. He is also a member of the IARC Advisory Committee. Dr. Brundtland's second move was to appoint Dr. Peter D. Jacobson as Deputy Director-General. Dr. Jacobson is a well-known epidemiologist and has been at IARC since 1980. He is also a member of the IARC Advisory Committee.

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THE LANCET, 2003, 361, 9245, 2003

Dr. Brundtland's 2003 resignation from the IARC Advisory Committee



It only needs the perception, let alone the reality, of financial conflicts and commercial pressures to destroy the credibility of important organisations such as IARC and its parent, WHO.

Is industry influencing IARC to downgrade carcinogens?

Dr. Peter D. Jacobson, Deputy Director-General of IARC, has been accused of being influenced by industry to downgrade carcinogens. Dr. Jacobson has denied these allegations, stating that he is an independent scientist and that his decisions are based on the scientific evidence.

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Lashed by Critics, WHO's Cancer Agency Begins a New Regime


The International Agency for Research on Cancer (IARC) has been criticized for its handling of the asbestos case. Critics have accused IARC of being influenced by industry to downgrade carcinogens. IARC has denied these allegations, stating that its decisions are based on the scientific evidence.

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These authors have frequently used this strategy with students, and the authors have had over 200 interactions between these two students.

and protected" procedures are long in vogue to minimize the possibility that special interests might otherwise be lobbying a legislative committee. Inexpensive participation devices—such as telephone hotlines, Web 2.0 sites, e-mail surveys, and other Web 2.0 sites—have been developed as one means, and is the preferred approach, experts with monitoring concerns have recommended, to allow participation, and in effect, to make the process more democratic.



See also: [Cognitive Psychology](#), [Developmental Psychology](#), [Educational Psychology](#), [Health Psychology](#), [Industrial Psychology](#), [Intelligence](#), [Personality](#), [Psychiatry](#), [Psychology](#), [Psychology of Women](#), [Social Psychology](#), [Theoretical Psychology](#)

hydroxyacids (for 33-35, 1986), as well as organophosphorus insecticides and various pesticides and metals. A limited study of the effects of these chemicals on the bacterial flora in sediments in the Baltic Sea (Lundström and Jönvall 1983) gave promising results. The composition of the bacterial flora was completely unaffected, even though the sediments were heavily polluted. As a consequence, the Baltic Sea Bacterioplankton might be the only bacterioplankton in the world which is not affected by the increasing presence of toxic organic pollutants in the environment. Along with the presence of any organisms as representatives of natural and transient faunal species, these sediments probably contain a variety of dormant organisms in the BSC within the so-called "seed" population. In the Baltic Sea, this will be a very

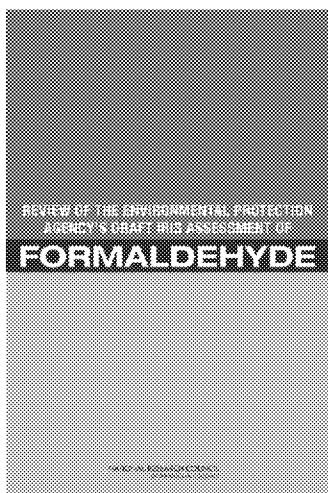
The joint announcement made by the United Nations and UNESCO in its 1988 year is an important step towards restoring trust in the war-torn nations of the world. The United Nations and UNESCO are the only two organizations in the world that have the authority to make such a statement.

Studies done by publicly funded agencies are less organized and reported. This theme was discussed in 1994. We estimate that only one and one half of the pilot initiative will serve as a model for other health agencies. Because the Washington programs have been ongoing and used public health implications, the United Kingdom estimated 50% reduction in infantile is not reported to children and are phased to have been given the opportunity to help improve transparency in 1995. > 1000 initiatives.

1

David Collingridge
Editor, *The Lancet Oncology*, London

An Alarm Bell for IRIS



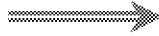
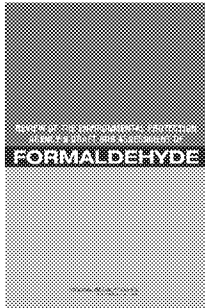
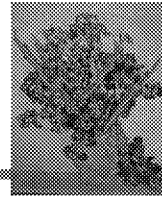
“ . . .recurring methodologic problems”

“ . . .problems with clarity and transparency of the methods appear to be a repeating theme over the years, . . .”

“ . . . the draft was not prepared in a consistent fashion; it lacks clear links to an underlying conceptual framework; and it does not contain sufficient documentation on methods and criteria . . .”

-p 4

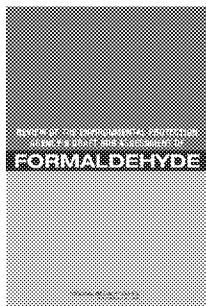
The NRC's "Roadmap for Revision": Adopt Systematic Review



“ . . . there are numerous examples of systematic approaches to hazard identification, including the monographs on carcinogenicity of the International Agency for Research on Cancer and the National Toxicology Program.”

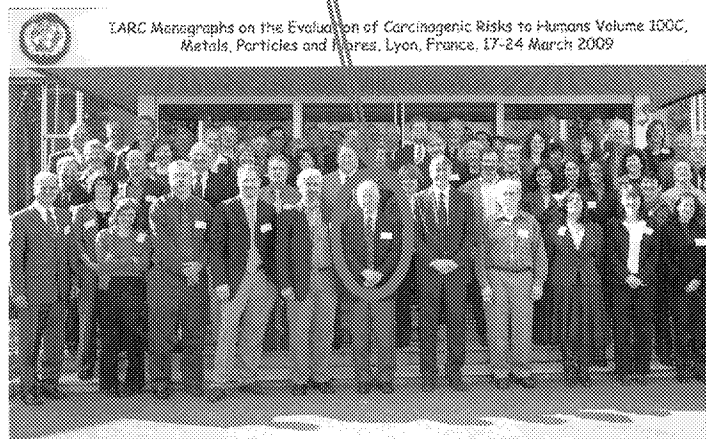
– p 160

The NRC's "Roadmap for Revision": Adopt Systematic Review



“... there are numerous examples of systematic approaches to hazard identification, including the monographs on carcinogenicity of the International Agency for Research on Cancer and the National Toxicology Program.”

– p 160



Each Monograph Has an Overview, Evidence Tables and Synthesis



Chromium (VI) compounds

workers at the beginning of their work shift less frequently, and at the beginning and end of their work shift for Friday. The geometric mean air concentration was 0.15 µg/m³ (range 0.04-0.33 µg/m³; range 0.02-1.5 µg/m³). Geometric mean creatinine levels were as follows: pre shift Monday, 0.43 mg/dL (0.40-0.53 mg/dL); pre shift Tuesday, 0.43 mg/dL (0.39-0.52 mg/dL); pre shift Wednesday, 0.45 mg/dL (0.41-0.51 mg/dL); pre shift Thursday, 0.45 mg/dL (0.41-0.51 mg/dL); pre shift Friday, 0.45 mg/dL (0.41-0.51 mg/dL).

2. Cancer in Humans

2.1 Introduction

A large number of case reports dating to the late 19th and early 20th centuries related symptoms that workers in various industries with exposure to chromium compounds, including chromate production, production of chromate pigments, and chromium plating, had had risk of developing various cancers (1,2,3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100).

The strongest evidence presented at the time concerned the lung. There was weaker and less consistent evidence of effects on gastrointestinal sites, mainly stomach, and on other parts of the respiratory tract, such as the larynx, trachea, and bronchi. Furthermore, there were case reports and small clusters of nasal or nasopharyngeal cancers in workers exposed

to chromium (VI). Based on the review of the previous IARC monograph and an subsequent review of relevant epidemiologic studies conducted since then, the Working Group revised the current review on these sites for which the evidence indicates possible associations with chromium (VI) compounds, mainly lung, nose and nasal sinus. Because of recent controversy regarding possible effects on stomach cancer (11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100), the Working Group also reviewed relevant evidence for this organ. For other organs, the number of reports of excess risks is unremarkable in the context of the numbers of studies that have been conducted, and no further comment is warranted.

There have been at least 20 epidemiological studies that could be informative about cancer risks related to chromium (VI). Many of the studies have gone on to multiple reports, sometimes these simply represent follow up updates, but often the different reports also present different types of analyses of subgroups or of case-control analyses within a cohort. Only a minority of the studies contain standardized measurements of chromium (VI) exposure, periodically measurements that pertain to the area of exposure of the workers that was investigated. It was therefore necessary to select and present the evidence according to the availability of relevant exposure information. The studies were triaged into the following categories:

1. Cohort studies in industries in which workers have higher likelihoods than general population of relatively high levels. The included studies in chromate production, chromate pigment production, and chromium electroplating.
2. Cohort studies in which workers were possibly exposed to relatively high levels but not with the same degree of certainty as concentration in those in category 1. This included stainless steel welders.
3. Other studies in which workers may have been exposed to chromium (VI), but with lower likelihoods than frequency or lower

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Based on review of the previous *Monograph* and subsequent epidemiology, focus on

- Lung
- Nose and nasal sinus
- Stomach (due to recent controversy)

At least 50 studies could be informative . . . A minority contain measures of Cr VI exposure . . . The studies were triaged:

1. Workers highly likely to be exposed to relatively high levels: chromate production, chromate pigment production, chromium electroplating.
2. Workers possibly exposed to relatively high levels: stainless steel welders.
3. Workers exposed with lower likelihood, frequency, or concentration: ferrochromium and stainless steel production, mild steel welding, general paint production, general spray painting, tanneries, gold mining, nickel plating.

Studies in category 3 not included because there were sufficient studies in categories 1 and 2.

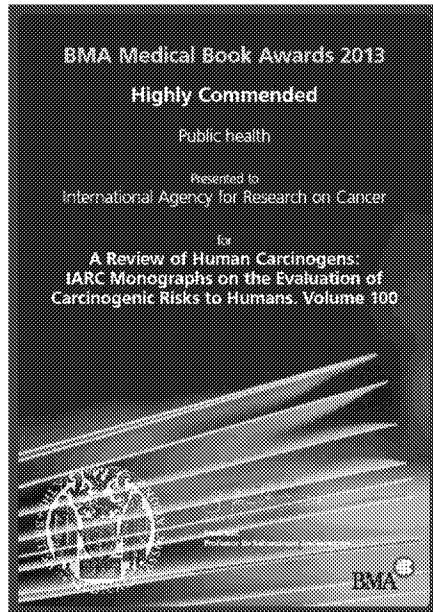
Each Monograph Has an Overview, Evidence Tables and Synthesis



Table 2.1. Cohort studies of chromium IV and lung and respiratory cancer

Author (year) Country	Characteristics of Cohort	Exposure Assessment	Cases	Exposure Category	n	Relative Risk	95% CI	Type of estimate and reference population
Hansen et al. (1989) Denmark	10,052 ex-Born, stainless steel smelters, and other non-ferrous metal melting companies, employed 1964-66; followed 1968-88	Strict quantitative on lifetime occupational and smoking status history. 83% response	Cohort partly included in Silkeborg study. Results for solid and malignant mesothelioma were distinct by cancer	All 55 nations	22	1.19	0.32-4.79	SMR ref. Denmark
Larsen et al. (1996) Norway	Seven cases control study; subset of 8,372 respondents of the Hansen et al. 1986 cohort; 51 lung cancer deaths occurring 1946-86, 439 controls	Occupation and smoking history based on mailed questionnaire	Unpublished findings at 1985 and 1991. Sørensen et al. 1991. Results for solid and malignant mesothelioma were distinct by cancer	All 55 nations	20	1.0	0.3-2.6	OR adjusted for smoking
Alexander et al. (1990) Washington state	24,226 response rate; 6 months' exposure to Cr(VI) employed 1940-81 and followed 1975-84	Industrial hygiene data and work history records, available for all years of the study		4 locations 19.5-191.7 elevated years	13 2	0.8 1.1	0.4-1.3 0.3-2.7	SMR ref. United States SMR ref. Puget Sound
Mikkelsen et al. (1993) Sweden	251 stainless steel workers from 5 different companies employed 1945-89, followed 1985-92	A job-exposure matrix for Cr(VI)		High exposure to Cr(VI)	6	1.64	0.42-7.58	SMR ref. Sweden
Rothman et al. (1991) Israel	1172 Jewish male workers from 1950 and later in 1955; followed 1955-89		They show that for solid cancer and leukemia Cr(VI) and not manganite (MnO ₂) is the cause	All 55 nations	29	1.24	1.04-2.15	SMR ref. Israel

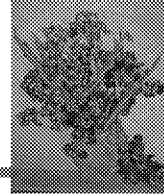
**“ . . . an authoritative statement
from an authoritative body.”**



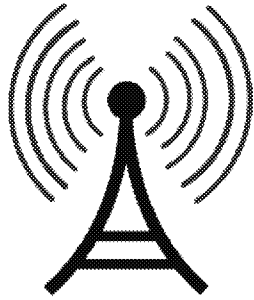
“This is an important resource in that it defines the current state of evidence-based thinking on cancer causing agents. It . . . meets its objectives very well and is an authoritative statement from an authoritative body.”

– British Medical Association, 2013

Another Alarm



"EPA science is on the rocks."

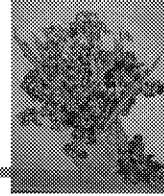


"You can't fail this time."

– statement to SAB and BOSC, 2011



Vision for IRIS:



- Our assessments are regarded as “an authoritative statement from an authoritative body”
- IRIS is the “Encyclopedia of environmental health hazards”
- [Become the company most known for changing the worldwide image of Japanese products as being of poor quality. Made in Japan will mean something fine and not shoddy – Akio Morita]

What IRIS Must Be



accurate

best-of-
its-kind

trusted

Authoritative

What IRIS Must Be



accurate

best-of-
its-kind

comprehensive

trusted

Authoritative
Encyclopedic

What IRIS Must Be



accurate
improved science

transparent

best-of-
its-kind

comprehensive
productive

trusted

Authoritative
Encyclopedic
“Enhancements”

What IRIS Must Be



accurate
improved science
credible

transparent
transparent

best-of-
its-kind

comprehensive
productive

trusted

inclusive

Authoritative
Encyclopedic
"Enhancements"
Thomas Burke

Systematic Review



accurate
improved science
credible



transparent
transparent



best-of-
its-kind

comprehensive
productive

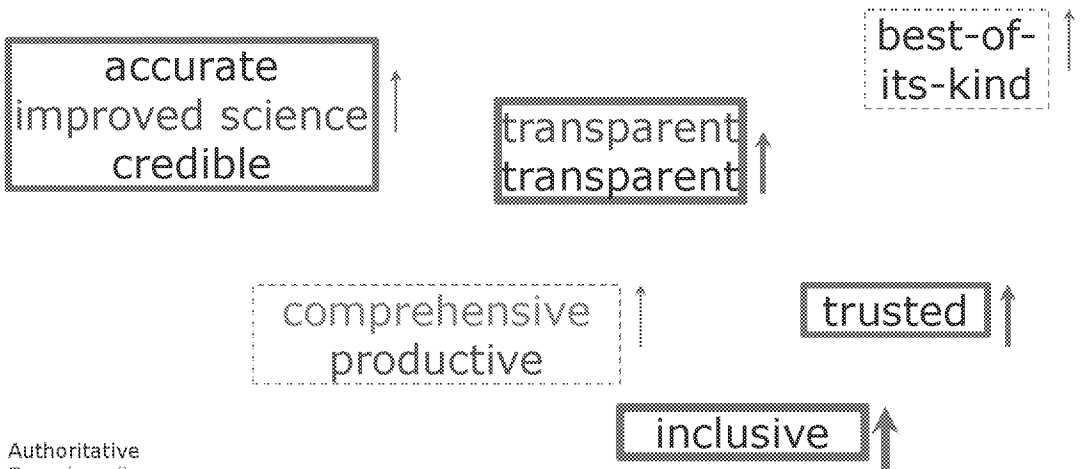
trusted



inclusive

Authoritative
Encyclopedic
"Enhancements"
Thomas Burke

Public Engagement



Authoritative
Encyclopedic
"Enhancements"
Thomas Burke

Consistent Peer Review



accurate
improved science
credible



transparent
transparent

best-of-its-kind



comprehensive
productive

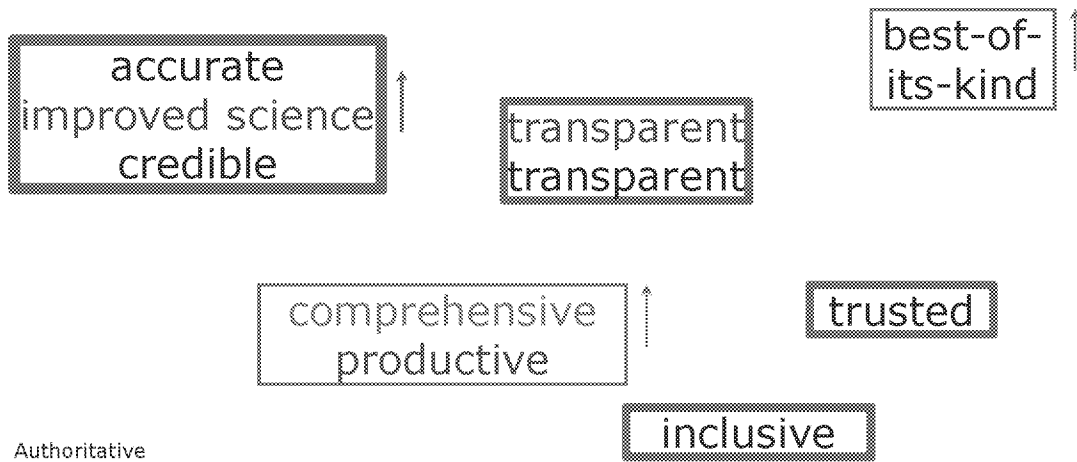
trusted



inclusive

Authoritative
Encyclopedic
"Enhancements"
Thomas Burke

Disciplinary Workgroups

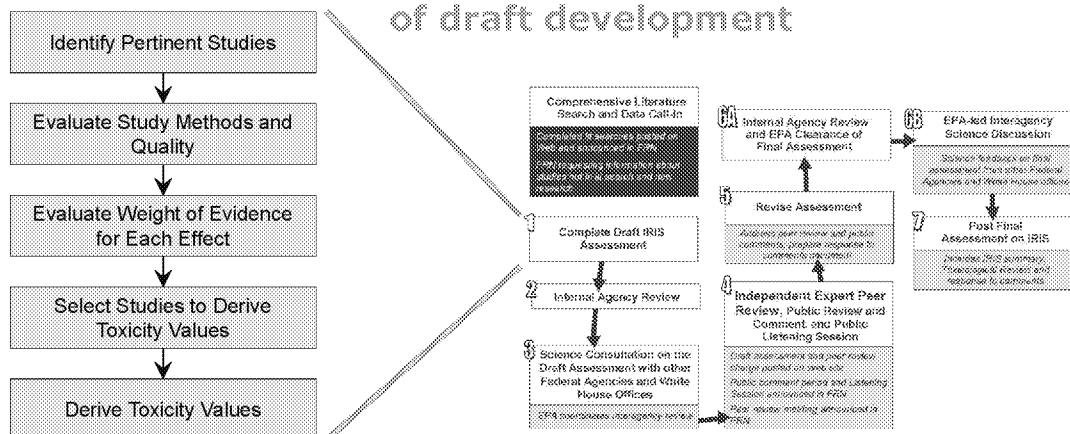


Authoritative
Encyclopedic
"Enhancements"
Thomas Burke

First Wave of Improvements: Adopting Systematic Review



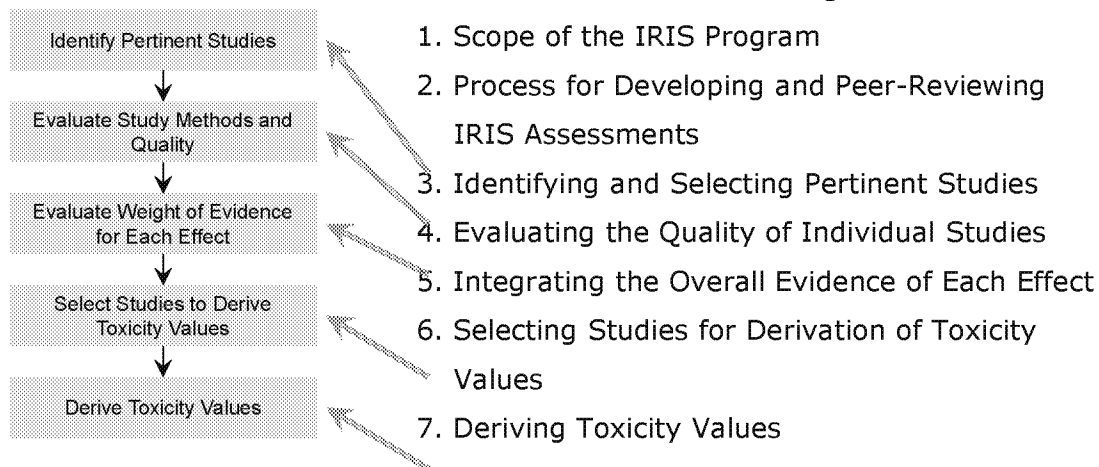
The NRC identified five stages of draft development



A New Preamble Explains How Assessments are Developed



Preamble to IRIS Toxicological Reviews



IRIS documents are becoming clear, concise, and systematic



Old structure

- Introduction (1/2 page)
- Literature search (1 page)
- Lengthy study summary narratives (all studies, many pages, detailed descriptions)
- Combined section with hazard identification and dose-response

Standard assessment: 300 pp

Complex assessment: 1000 pp

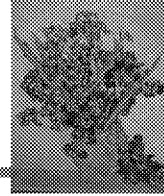
New structure

- Preamble (15 pages)
- Detailed literature search strategy
- Evidence tables of key studies for each adverse effect
- Identification of health hazards
- Toxicity values for each health hazard

Standard assessment: 100 pp

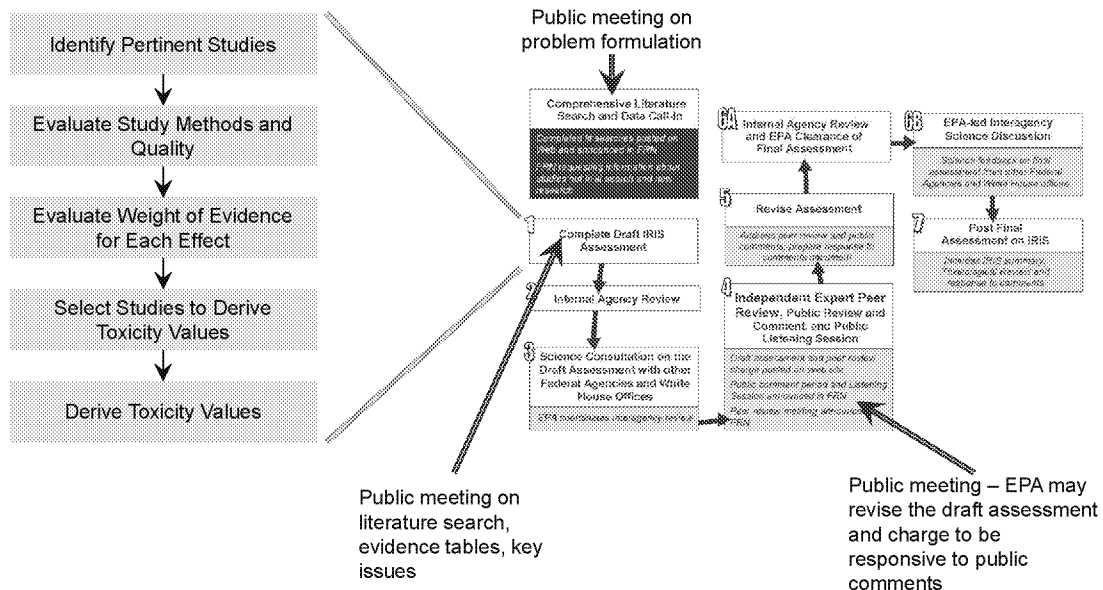
Complex assessment: 200 pp

Simultaneously, New Science Content Has Been Added



- Hazard section to identify credible health hazards
 - Weight-of-evidence categories for noncancer effects will be evaluated after the NRC's advice in June 2014
- Toxicity values are explored for each credible health hazard
 - This will facilitate subsequent cumulative risk assessments that consider the combined effect of multiple agents acting at a common site or through common mechanisms

Second Wave of Improvements: Increasing Public Engagement



Second Wave of Improvements: Frequent Scientific Workshops



- Recent workshops
 - Systematic review (Aug 2013)
 - Hexavalent chromium (Sept 2013)
- Upcoming workshops
 - Mouse lung tumors (Jan 2014)
 - Formaldehyde (TBD)
 - Issues for endogenous chemicals (TBD)
- Preparations include a public call for topics and speakers
- Webinar format enhances public access

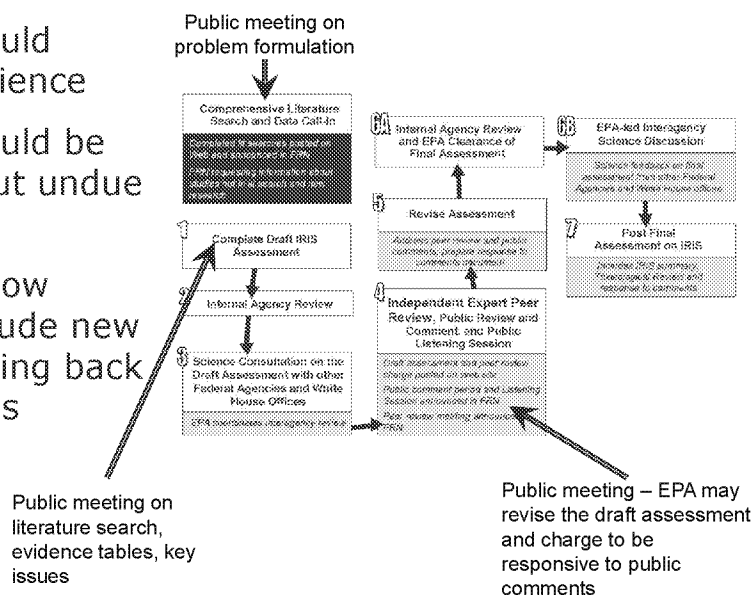
Second Wave of Improvements: Bringing Assessments to Completion



Two conflicting ideals:

- Assessments should reflect current science
- Assessments should be completed without undue delay

“Stopping Rules” allow assessments to include new studies without cycling back through earlier steps

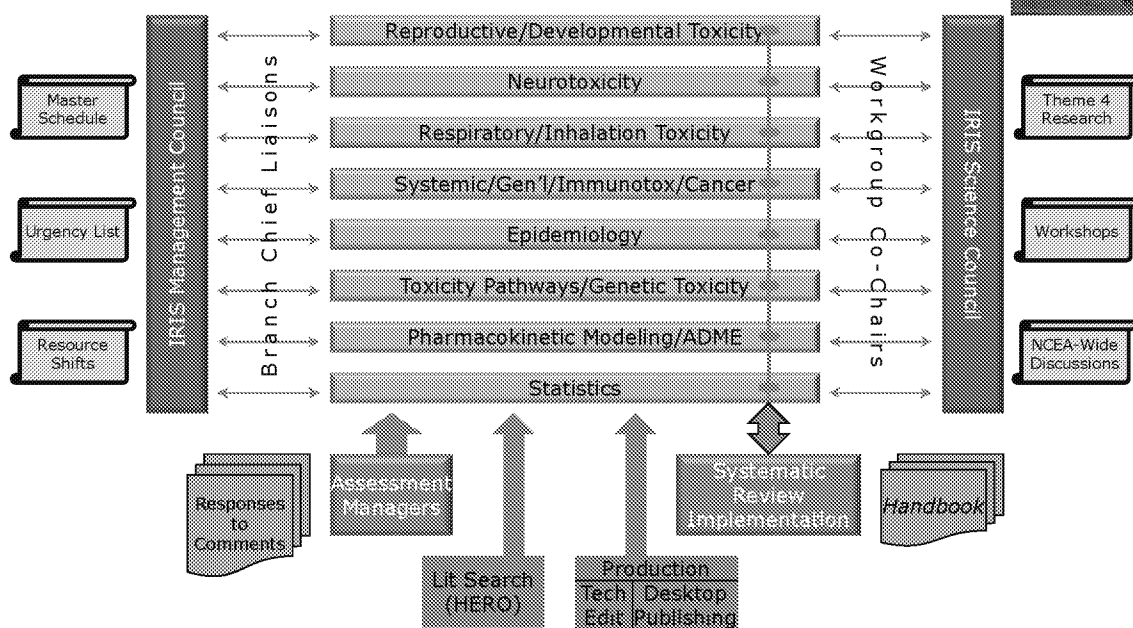


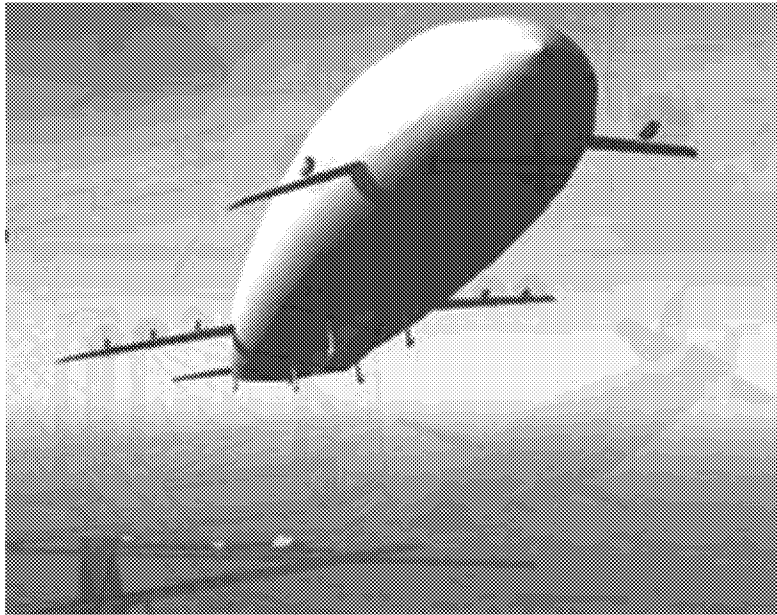
New Internal Workflow for Draft Development



- Disciplinary Workgroups will do most analysis and writing
- IRIS Science Council
 - Represents all assessment disciplines
 - Addresses major science issues
 - Identifies topics for workshops or further research
- IRIS Management Council
 - Represents all management levels across four divisions
 - Maintains Master Schedule of assessments
 - Maintains Urgency List of assessments
 - Shifts resources across assessments and workgroups

New IRIS Workflow Structure





Good for the Program; Good for Career Development



GOOD for the Program

- Increased consistency across program
- Fewer “units” to manage
- Ability to identify critical personnel needs and target relief to those areas
- Structure to bring in scientists on a short-term or part-time basis

GOOD for Career Development

- Broader experience – see many more assessments
- Learn from others in the same field
- Increased opportunities to write papers
- Increased opportunities to manage work, run meetings, learn to build consensus

IRIS Mission



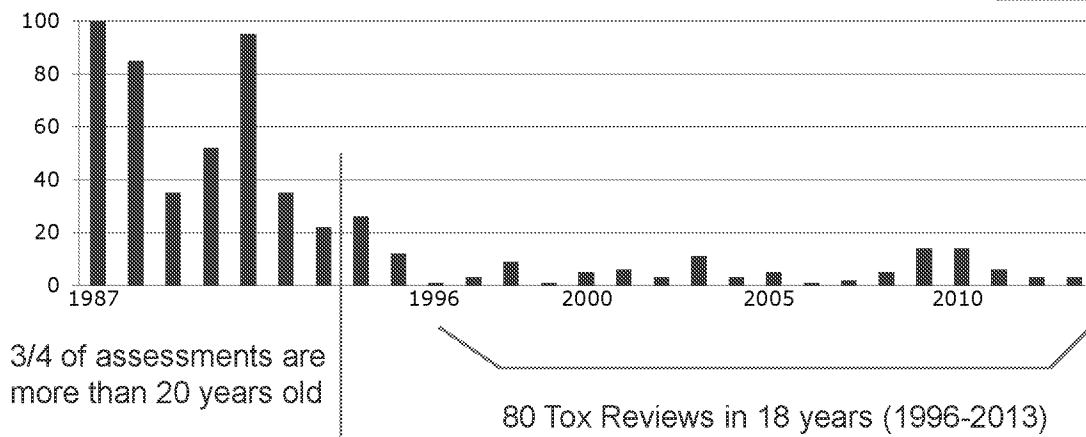
- To develop Tox Reviews
- that the scientific community regards as authoritative
- with full public participation

Enhancements to IRIS



- IRIS is making changes to
 - Improve the fundamental science
 - Improve the productivity of the program
 - Increase transparency so issues are identified and debated early
- These changes span three broad areas
 - Use of systematic review methods
 - Enhancements to the 7-step IRIS process
 - New internal workflow for draft development

IRIS Postings by Year

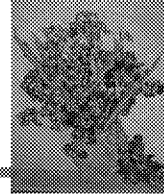


Objectives of the New IRIS Enhancements



- **To improve the fundamental science**
 - by adopting the principles of systematic review
 - by strengthening peer review
- **To increase productivity** to better meet stakeholder needs
- **To increase transparency** so issues are identified and debated early

Some Challenges for 2014



- Increase productivity
 - Since 1996, 4-5 assessments/year
 - We expect to triple productivity within 2-3 years

- Begin implementation of Problem Formulation
 - Coming soon in early 2014!

- Implement a new internal workflow to better achieve IRIS's objectives of improved science and increased productivity

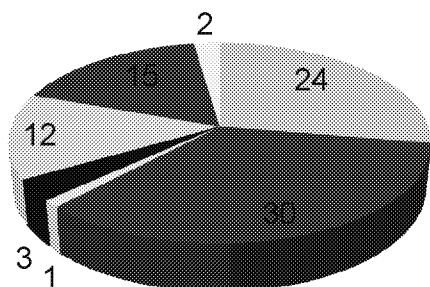


Some future initiatives

Ensuring Success: Make Public Meetings More Inclusive



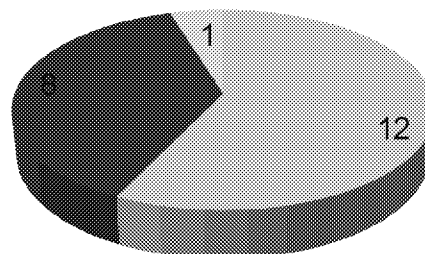
**Affiliations of attendees
for Dec 2013**



- Industry/Trade assoc
- NGOs
- Other federal gov't
- Media
- Consultants
- Academia
- State/Local/Tribal gov't

Plus 76 from EPA

**Affiliations of speakers
for Dec 2013**



- Industry/Trade assoc
- NGOs
- Other federal gov't
- Media
- Consultants
- Academia
- State/Local/Tribal gov't

Making Public Meetings More Inclusive



OLD MEETING FORMAT

- Assessment A
 - Speaker 1
 - Speaker 2
- Assessment B
 - Speaker 1
 - Speaker 2 (yields to Speaker 1)
 - Speaker 3 (yields to Speaker 1)
 - Speaker 4 (yields to Speaker 1)
- Assessment C
 - Speaker 1
- General comments

Making Public Meetings More Inclusive



~~OLD MEETING FORMAT~~

- ~~– Assessment A
 - ~~• Speaker 1~~
 - ~~• Speaker 2~~~~
- ~~– Assessment B
 - ~~• Speaker 1~~
 - ~~• Speaker 2 (yields to Speaker 1)~~
 - ~~• Speaker 3 (yields to Speaker 1)~~
 - ~~• Speaker 4 (yields to Speaker 1)~~~~
- ~~– Assessment C
 - ~~• Speaker 1~~~~
- ~~General comments~~

We can do
better!

Making Public Meetings More Inclusive



NEW MEETING AGENDA

- Assessment A
 - Issue 1
 - Issue 2
 - Issue 3
 - Assessment B
 - Issue 1
 - Issue 2
 - Assessment C
 - Issue 1
 - Issue 2
 - Open forum & discussion
- STEP 1. 2-4 months before a meeting:
- Post preliminary agenda based on issues
 - Post materials for each assessment

Making Public Meetings More Inclusive



NEW MEETING AGENDA

– Assessment A

- Issue 1
- Issue 2
- Issue 3

STEP 1. *2-4 months before a meeting:*

- Post preliminary agenda based on issues
- Post materials for each assessment

– Assessment B

- Issue 1
- Issue 2

STEP 2. *Up to 1 month before the meeting:*

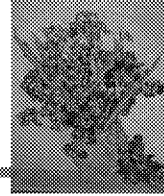
- Receive public requests to speak on issues
- Encourage scientific experts and under-represented sectors to nominate themselves
- Receive suggestions for additional issues

– Assessment C

- Issue 1
- Issue 2

– Open forum & discussion

Making Public Meetings More Inclusive



NEW MEETING AGENDA

– Assessment A

- Issue 1
- Issue 2
- Issue 3
- Issue 4

STEP 1. *2-4 months before a meeting:*

- Post preliminary agenda based on issues
- Post materials for each assessment

– Assessment B

- Issue 1
- Issue 2

STEP 2. *Up to 1 month before the meeting:*

- Receive public requests to speak on issues
- Encourage scientific experts and under-represented sectors to nominate themselves
- Receive suggestions for additional issues

– Assessment C

- Issue 1
- Issue 2
- Issue 3

STEP 3. *Up to 1 month before the meeting:*

- Find a speaker for any issue where scientific expertise or balance is lacking

– Open forum & discussion

Making Public Meetings More Inclusive



NEW MEETING AGENDA

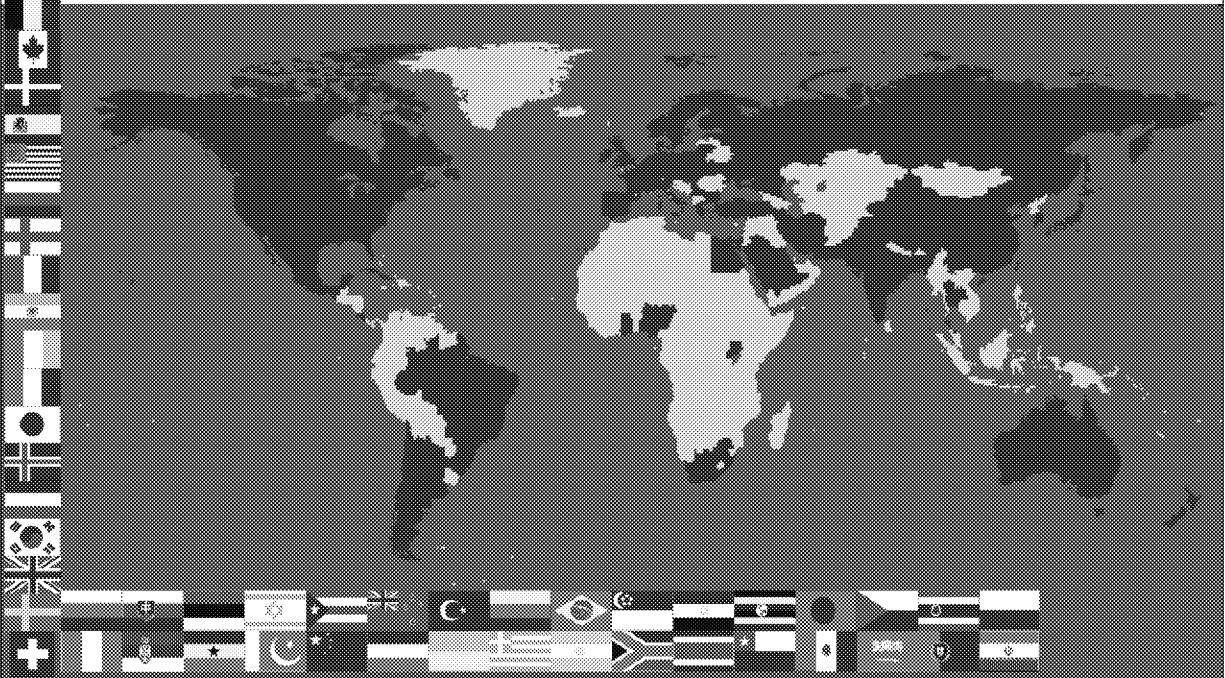
- Assessment A
 - Issue 1 speakers
 - Issue 2 speakers
 - Issue 3 speakers
 - Issue 4 speakers
 - Assessment B
 - Issue 1 speakers
 - Issue 2 speakers
 - Assessment C
 - Issue 1 speakers
 - Issue 2 speakers
 - Issue 3 speakers
 - Open forum & discussion
- STEP 1. *2-4 months before a meeting:*
- Post preliminary agenda based on issues
 - Post materials for each assessment
- STEP 2. *Up to 1 month before the meeting:*
- Receive public requests to speak on issues
 - Encourage scientific experts and under-represented sectors to nominate themselves
 - Receive suggestions for additional issues
- STEP 3. *Up to 1 month before the meeting:*
- Find a speaker for any issue where scientific expertise or balance is lacking
- STEP 4. *A few days later:*
- Post timetable and speakers' names

Ensuring Success: Involve 200 Scientists over the Next 5 Years

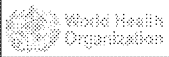


- Workshops
- Bimonthly public meetings
 - In April, begin to involve unaffiliated academics
- Disciplinary workgroups

You are part of a worldwide endeavour that since 1971
has involved over 1200 scientists from 53 countries



International Agency for Research on Cancer



Ensuring Success: Complete Assessments; Keep Them up to Date



Consider these scenarios . . .

- Pressure increases to re-examine the developmental effects of trichloroethylene
- NCI updates its epi study as the acrylonitrile assessment is about to be posted
- NTP announces it will undertake a chronic inhalation study for PCBs
- New studies contribute substantially to knowledge about mechanistic pathways for formaldehyde-induced leukemia

These Have a Common Solution: Modular Assessments



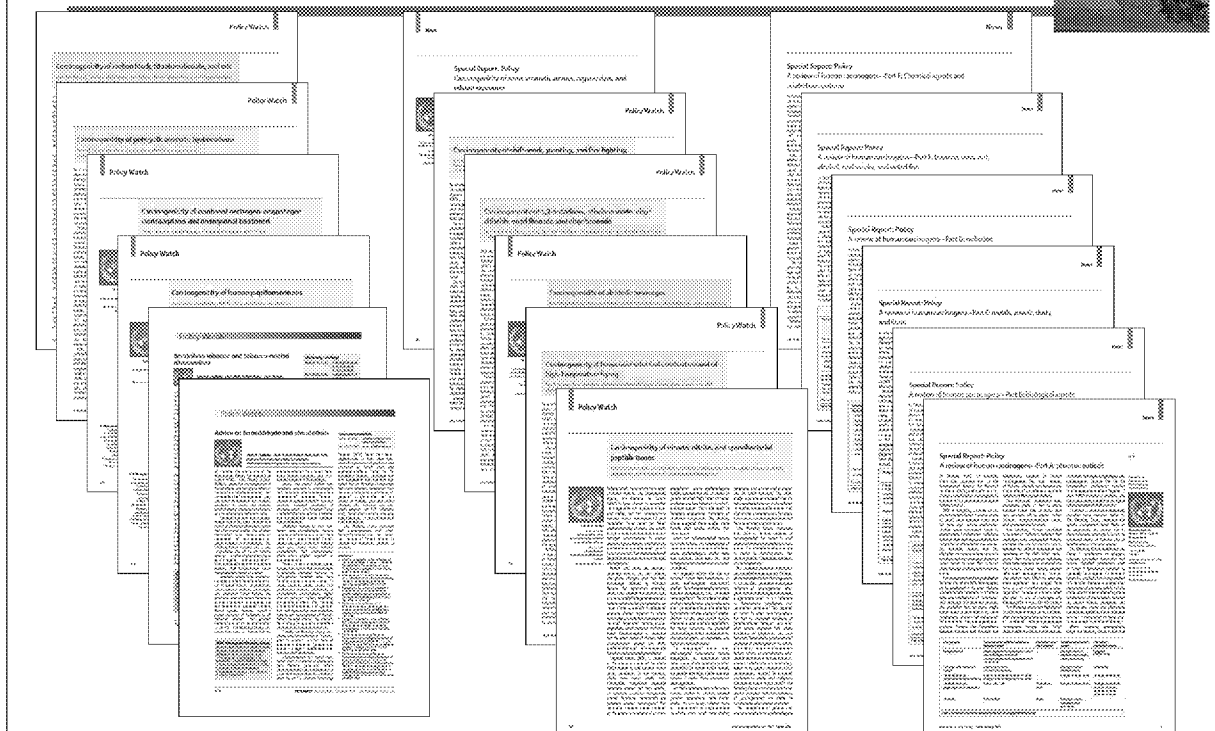
- Front matter
- Hazard identification
 - Cancer
 - Reproductive toxicity
 - Neurotoxicity ←
 - Immunotoxicity
 - Hepatotoxicity
- Dose-response analysis
 - Organ/system RfDs ←
 - Overall RfD ←
 - Organ/system RfCs
 - Overall RfC
 - Cancer slope factor
 - Cancer unit risk
- A new neurotoxicity study?
- Update just these sections:
 - Neurotox lit search
 - Neurotox evidence tables
 - Neurotox RfD
 - Overall RfD (possibly)
 - and the *revision dates* for these sections

How Modular Assessments Could Work



If . . .	Then . . .
Pressure to re-examine developmental effects of trichloroethylene	Re-do only the developmental hazard and developmental toxicity values
NCI updates epi study as acrylonitrile assessment is about to be posted	POST the assessment; re-do cancer sections when study is published
NTP announces it will undertake a chronic inhalation study for PCBs	FINISH the oral assessment; add inhalation hazard and RfC later
Mechanistic pathway for formaldehyde-induced leukemia	FINISH rest of the assessment; then update the leukemia section

Ensuring Success: Increase Publications



Human Health Effects of Trichloroethylene: Key Findings and Scientific Issues

ED 002435 00003558-00051



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Winters, James; Cogliano, Robert; Cook, Ken; Cook, Tami; Duvalla, Mylene; Lundy-Greenlee, Paula; O'Quinn, Myron; R. Edwards, Lennie; Seabright, John; Smith, David; Thomas, Donald; Pearson, Louise; Gifford, Christopher. © 1994.

Manuscript received November 16, 2015; revised October 12, 2016; accepted October 14, 2017.

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Monitors are the backbone of a specific task or important business process (e.g., access requests, access control, and case logging, etc.). The *Interpersonal Supply for Information on Cases* (ISIM) Storage applications, which has been created for case managers for more than 15 years, recently managed to receive a wide-scale information on the cases they access and from more than 150,000 agents. Based on ISIM's mission to make this source of data accessible with their agents and to make it available to the management, the ISIM team has been working on a new version of the application. The new version for visualization that were built on *Microsoft* data. The first milestone, based on the *Microsoft* ISIM Management System, has other changes, like the *Microsoft* data structure of the application architecture. Due to *Microsoft*'s security architecture, a technology and architecture needed to identify additional categories of cases such as conflicting cases, the involvement of user support, *Microsoft* storage applications, and other data that have been used to identify access agents.

J. Appl. Comput. Graph. 30(1):52-58, 2002. © 2002.

[illegible]

Summary. The International Agency for Research on Cancer (IARC) classified a group of 10 of the more than 100 herbicides, pesticides, physical agents, industrial agents, and other agents that are classified as carcinogenic to humans (Group 1, IARC) as agents that are thought to increase (Group 2, probable carcinogenic) or decrease (Group 3, possibly carcinogenic to humans [IARC 2012]) the risk of developing cancer. The IARC 2012 report also classified 17 agents as probably or possibly not carcinogenic to humans (Group 4 or 5). In the case, IARC estimated the "Working Group" that included 10 members from 20 countries in addition from published information and experimental studies, in contrast, the carcinogenicity of each agent, as IARC's report was not a usual assessment of a chemical or a product, and accordingly no toxicological studies were conducted. It is assumed. This work will be published in 2014 or 2015.

These two studies were the first in identifying cancer cases associated with agents, with some indications regarding dose-response with some agents for regular smokers, but no specific information with cancer is taken from *Table 2*. The state of the science is therefore to indicate a low degree of scientific certainty, or a false negative in most cases (concomitant exposure, or especially, no exposure without being aware of it) in several cases, as the case of asbestos (11). IARC has taken the exposure time and not tobacco intake periods into account, period of 100 years.

In addition to the above, we have also reported that the cancer risk is influenced by many other DNA-based carcinogens classified through 50 years of IARC Monographs review, even though the information on the chemical and biological nature of cancer is limited. In contrast, the chemical and biological nature of cancer is well understood in the case of the majority of carcinogens, carcinoblasts. Other factors associated with an increased cancer risk are covered in the IARC Monographs, mostly genetic, environmental, and lifestyle factors, and some biological factors, are not included in the review.

For each agent, the *ABC* character is an aggregate measure, an averaged line of the scores that for which we have traditional evidence of "biased behavior" (an excessive, or excessive, "disposition" of this agent). *ABC* is a score in the range from 0 to 100, with 0 representing a neutral, unbiased, or unbiased, and 100 representing a strong, biased, or biased, disposition.

DOI : 10.1002/for

- Environmental causes of human neurotoxicity
- Environmental causes of reproductive toxicity
- Environmental causes of emerging diseases
- etc

Good for the Program; Good for Career Development



GOOD for the Program

- Increased dissemination of IRIS findings and views
- Perceived endorsement by top scientific journals
- Increased recognition of IRIS as a scientific program
- Increased reputation of IRIS scientists
- Increased credibility of assessments
- Increased ability to attract new talent

GOOD for Career Development

- More publications
- More invitations to scientific meetings
- More interaction with the scientific community
- Enhanced scientific reputation

. . . TQB

Ensuring Success: **Continuity during Election Years**




- Consider
 - Scientific journals published by NIH institutes
 - Monthly Unemployment Rates and Consumer Price Index from the DOL/BLS
- Why can't IRIS be like that?
- *Ensuring success*
 - Achieve authoritative status
 - Achieve regularity of outputs
 - Scientific oversight independent of politics

Ensuring Success:
Partner with Other Federal Agencies



A Mark of Success: **Leaving the GAO's High-Risk List**



2008	Low productivity OMB-led interagency review	
2011	Continued low productivity Unaddressed issues with clarity and transparency of assessments Outdated information on status of ongoing assessments	
2013	No recent evaluation of needs for IRIS assessments Need for criteria for selecting chemicals for assessment	
<hr style="border-top: 1px dashed black;"/>		
2009	<i>High-risk area</i> needing broad-based transformation to address major economy, efficiency, or effectiveness challenges	

How Does IRIS Get Off the GAO's High-Risk List?





QUESTION: Are we the sole arbiters of our guidelines?

OR

Can we accept peer review advice on how to interpret data relative to our guidelines?

Our Guidelines Envision Flexibility



"In summary, one objective of the RfC methodology is that it **always be scientifically based**, and thus, the **methodology should be considered dynamic**." [RfC methodology, 1994]

"In particular, the Guidelines emphasize that risk assessments will be conducted on a case-by-case basis, giving full consideration to all relevant scientific information. This approach means that Agency experts study scientific information on each chemical under review and **use the most scientifically appropriate interpretation** to assess risk." [Neurotoxicity guidelines, 1998]

"EPA cancer risk **assessments may be conducted differently than envisioned in the cancer guidelines** for many reasons, including (but not limited to) new information, new scientific understanding, or new science policy judgment. The science of risk assessment continues to develop rapidly, and specific components of the cancer guidelines may become outdated or may otherwise **require modification in individual settings**. Use of the cancer guidelines in future risk assessments will be based on decisions by EPA that the approaches are suitable and appropriate in the context of those particular risk assessments. These **judgments will be tested through peer review, and risk assessments will be modified to use different approaches if appropriate**." [Cancer guidelines, 2005]

"Where EPA does use the approaches in the Supplemental Guidance in developing risk assessments, it will be because EPA has decided in the context of that risk assessment that the approaches from the Supplemental Guidance are suitable and appropriate. This **judgment will be tested through peer review, and the risk assessment will be modified to use different approaches if appropriate**." [Early-life exposure guidance, 2005]

– [Emphasis added in all quotations]



**QUESTION: In each year, would we rather
complete**

4 assessments that satisfy us

OR

**20 assessments that satisfy the scientific
community?**

Ensuring Success for IRIS



- Make public meetings more inclusive
- Involve 200 scientists over the next 5 years
- Complete assessments; keep them up to date
- Increase publications
- Partner with other federal agencies

We're on a good path . . .

Thank you for your commitment

Summary of the IRIS Enhancements



Improved science

- IRIS has adopted systematic review
- New Hazard section identifies all credible health hazards
- Toxicity values are explored for each credible health hazard
- Peer review has been strengthened

Increased transparency

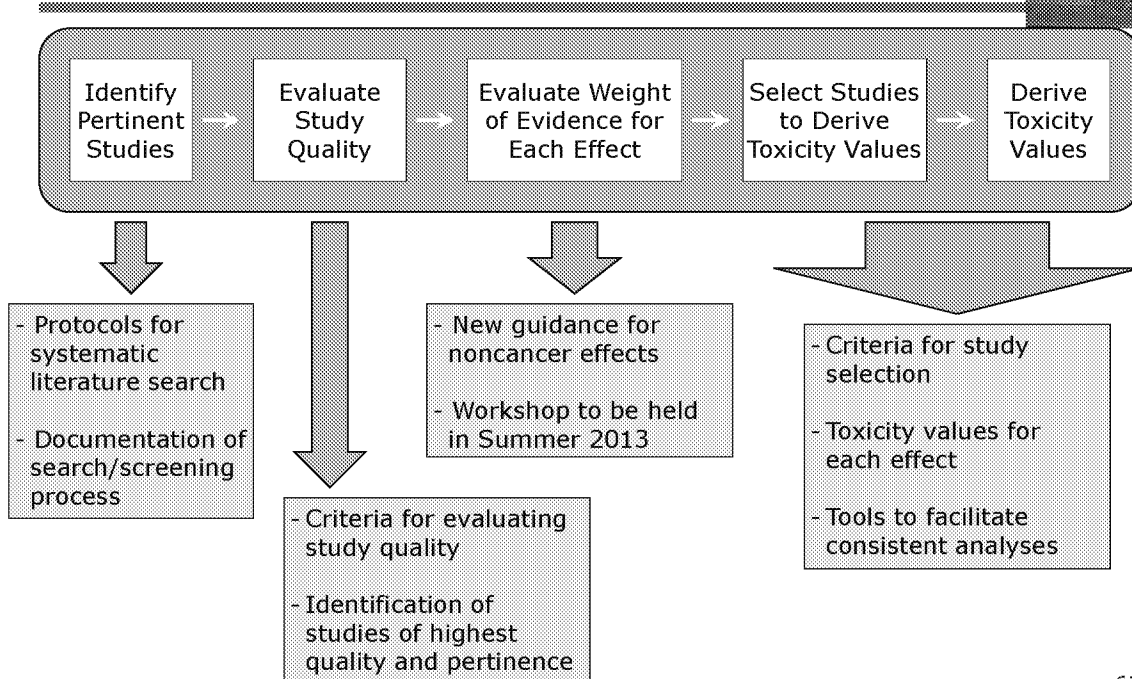
- Assessments are becoming clear, concise, and systematic
- IRIS is committed to early public engagement
- 2-3 opportunities for public engagement before peer review
- Frequent scientific workshops

Increased productivity

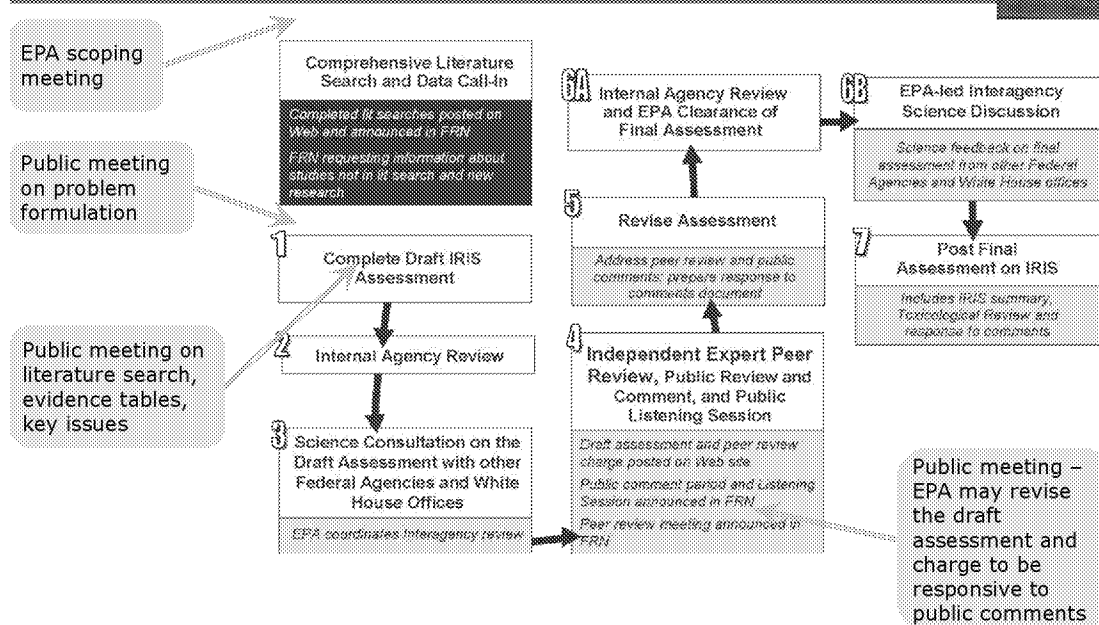
A major challenge for 2014-2015 will be to complete more assessments in less time

IRIS will continue to evolve as we receive public input and peer review advice – Thank you!

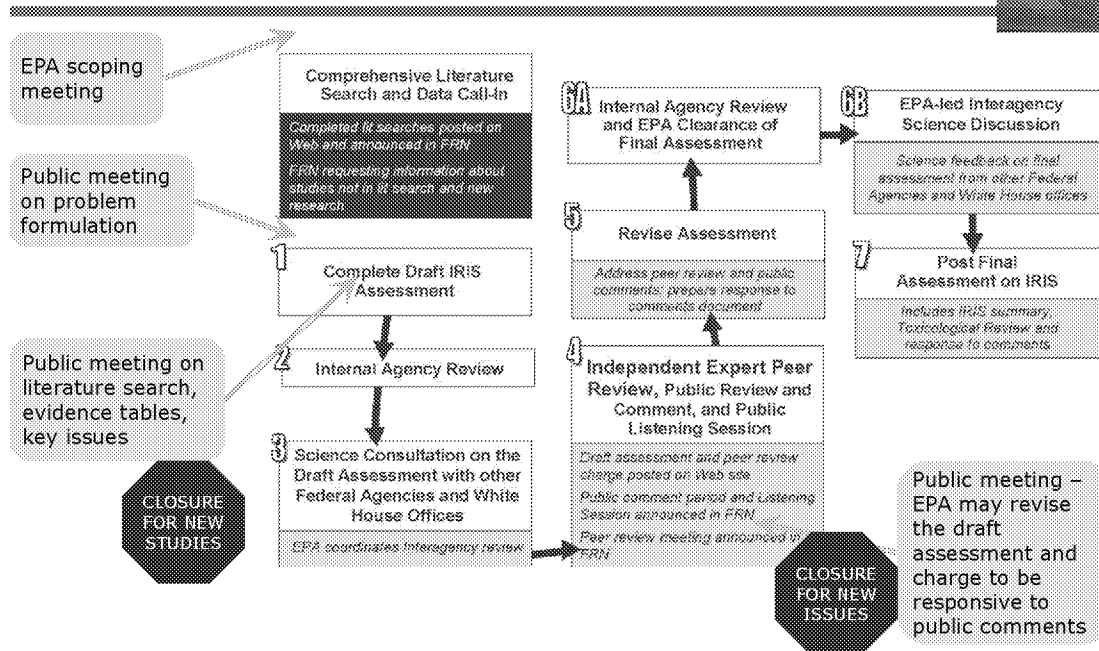
Use of Systematic Review Methods at Every Step of Draft Development



Enhancements to the 7-Step IRIS Process



Enhancements to the 7-Step IRIS Process

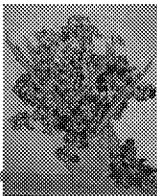


Peer Review Will Be More Robust



- There is a new Science Advisory Board committee – the *Chemical Assessment Advisory Committee* – dedicated to reviewing IRIS assessments
- EPA has also strengthened its process for contractor-managed peer review to better address conflicts of interests

Summary: IRIS is Changing for the Better



	Use of Systematic Review	7-Step Process Enhancements	New Internal Workflow
Improved science	✓✓	✓✓	✓✓
Improved productivity	✓	✓	✓✓
Increased transparency	✓✓	✓✓	

Comparison of Old and New Document Structures

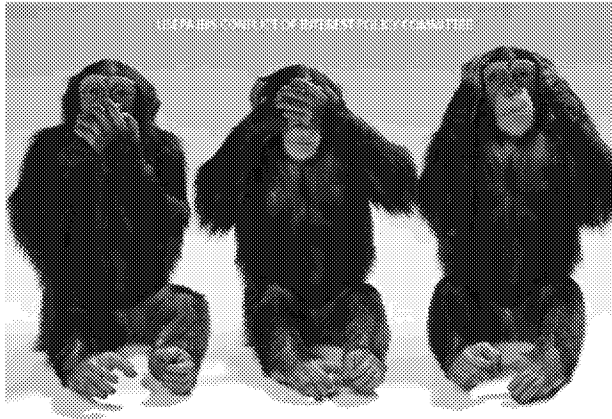


1 Introduction
2 Chemical and Physical Information
3 Toxicokinetics
4 Hazard Identification
(study-by-study summaries written in paragraphs)
4.1 Human studies
4.2 Subchronic and chronic animal studies and cancer bioassays
4.3 Reproductive and developmental studies
4.4 Other duration-or-endpoint-specific studies
4.5 Mechanistic data and other studies
4.6 Synthesis of major noncancer effects
4.7 Evaluation of carcinogenicity
4.8 Susceptible populations and life-stages
5 Dose-Response Assessments
(focus on most sensitive toxicity value)
- Overall RfD and RfC
- Oral slope factor; inhalation unit risk
6 Major Conclusions
6.1 Human hazard potential
6.2 Dose response
References

Preface (what and why for this assessment)
Preamble (general methods for IRIS)
Executive Summary
Literature Search / Study Selection
1 Hazard Identification
- Synthesis of evidence (by effect)
(focus on high-quality studies, tabular display)
- Summary and evaluation
2 Dose-Response Assessment
(focus on credible effects, high-quality studies)
- Organ/system-specific toxicity values
- Overall RfD and RfC
- Oral slope factor; inhalation unit risk
- (. . . others)
References
Supplemental Information
- Toxicokinetics and models
- Dose-response models

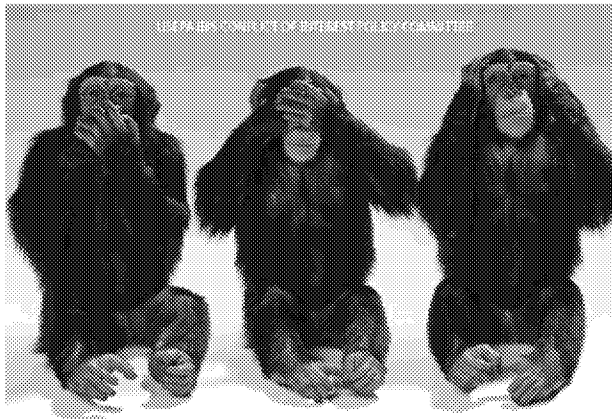
↑ <200 pages

← could be >1000 pages



<http://www.wolfenotes.com/2012/03/epa-caves-in-to-chemical-industry-pressure-on-chromium-drinking-water-standard/>

6 Mar 2012



In May 2013 the changes I implemented at IARC were adapted as a model for peer review panels across the EPA.

<http://www.wolfenotes.com/2012/03/epa-caves-in-to-chemical-industry-pressure-on-chromium-drinking-water-standard/>

6 Mar 2012